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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/032,281

12/21/2001

John Wyrick

10050560-1

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04/20/2006

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EXAMINER

FREDMAN, JEFFREY NORMAN

ART UNIT

PAPER NUMBER

1637

DATE MAILED: 04/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/032,281	Applicant(s) WYRICK ET AL.	
	Examiner Jeffrey Fredman	Art Unit 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on March 9, 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6,8-11,15-26,28-43,45-59 and 61-86 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6,8-11,15-26,28-43,45-59 and 61-86 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 9, 2006 has been entered.

Claim Interpretation

2. The claims now modify the term "intergenic" by indicating that an "intergenic" regions is "upstream of transcribed regions". This modification does not affect the applicability of the Orlando reference since Orlando teaches sequences (as shown in figure 7), which are upstream of transcribed regions. For example, the MCP site is upstream of the transcribed region of abdominal-B. Every sequence that is itself not transcribed, (and is not at the 3' terminal telomere of the chromosome), is necessarily upstream of some transcribed region. Thus, the sequences of Orlando and Mercola continue to meet this limitation as reasonably interpreted.

Response to Arguments – Claim interpretation

3. Applicant's arguments filed March 9, 2006 have been fully considered but they are not persuasive.

Applicant has amended the term "intergenic" to refer to the region as "upstream of transcribed regions". As noted in the claim interpretation, this does not have any effect on the prior art since every region will inherently have this property.

Applicant has also amended the term "microarray" to indicate that specific spots are identified. The examiner agrees that this now distinguishes over the Southern blot type analysis of Orlando and will necessitate a new 103 rejection teaching the desirability of microarrays.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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6. Claims 1-6, 8, 10, 11, 17-22, 39-43, 45, 48-53, 56-59, 61, 64-68, 71-76 and 78-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Orlando et al (Methods (1997) 11:205-214) in view of Schena (Tibtech (1998) 16:301-306).

Orlando teaches a method of claims 1, 10, 11 and 71 for identifying a region of a genome of a cell to which a protein of interest binds (see abstract) comprising the steps of:

a) crosslinking DNA binding proteins in the cell to genomic DNA of the cell, thereby producing DNA binding protein crosslinked to genomic DNA (see figure 1 and page 205-206, subheading "1. In vivo Formaldehyde fixation of cells"),

b) generating DNA fragments of the genomic DNA crosslinked to DNA binding protein in a), thereby producing a mixture comprising DNA fragments to which DNA binding protein is bound (see figure 1 and page 206, subheading "2. Chromatin solubilization by sonication"),

c) removing a DNA fragment to which the protein of interest is bound from the mixture produced in b) (see figure 1 and page 209, subheading "5. Immunoprecipitation of crosslinked chromatin"),

d) separating the DNA fragment identified in c) from the protein of interest (see figure 1 and page 210, subheading "6. Reversal of cross-links and DNA purification"),

e) amplifying the DNA fragment of d) (see figure 1 and page 210-211, subheading "8. Amplification of immunoprecipitated DNA by linker modified DNA PCR"),

f) combining the DNA fragment of e) with DNA comprising sequences complementary to intergenic regions of genomic DNA of the cell under conditions in

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which hybridization between the DNA fragments and a sequence complementary to an intergenic region of the genomic DNA occurs (see figure 1 and subheading "9. southern analysis and mapping of binding sites in DNA" where the figures 6 and 7 demonstrate that intergenic regions are on the blot as shown by the presence of probes such as probe 2206 which is between the ultrabithorax and abdominal-A genes),

g) identifying the one or more sequences complementary to the one or more intergenic regions of genomic DNA of f) to which the DNA fragment hybridizes whereby the region identified in g) is the region of the genome in the cell to which the protein of interest binds (see figure 1, page 211, column 2 and figures 6 and 7).

With regard to claims 1, 10, 11 and 71, Orlando teaches hybridization to a southern blot, which is a type of microarray as discussed above (see figure 6).

With regard to claims 2, 39, 56, 72, Orlando teaches the use of *Drosophila melanogaster* cells which are eukaryotic (see page 205, column 1).

With regard to claims 3, 40, Orlando teaches the use of DNA binding transcription factors (see page 213, column 2).

With regard to claims 4, 41, 57, 73, Orlando teaches crosslinking with formaldehyde (see page 205-206, subheading "1. In vivo Formaldehyde fixation of cells").

With regard to claims 5, 42, 58, 74, Orlando teaches the use of antibodies to bind the protein of interest (see page 209, subheading "5. Immunoprecipitation of crosslinked chromatin").

With regard to claims 6, 43, 59, 75, Orlando teaches the use of a ligation mediated PCR since the linkers must be ligated prior to PCR (see page 210-211, subheading "8. Amplification of immunoprecipitated DNA by linker modified DNA PCR").

With regard to claims 8, 45, 61, 76, Orlando teaches the use of a control (see figure 7, figure legend "The white bars indicate the fragments containing repetitive elements (M-repeats) that hybridized also with the control fraction").

With regard to claims 17, 48, 64, 79, Orlando teaches shearing the DNA to make fragments (see page 206, subheading "2. Chromatin solubilization by sonication").

With regard to claims 18-22, 49-53, 65-68, 80-84, Orlando teaches the entire upstream and downstream regions of the abdominal-A gene which inherently includes promoter and regulatory regions for abdominal-A and abdominal-B.

Orlando does not teach substitution of a DNA microarray with specific spots for the Southern blot used for detection in step (f).

Schena teaches the use of microarrays to analyze genomic information (see abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the microarrays of Schena for the Southern blot of Orlando since Schena expressly notes "Although reminiscent of filter based assays, chip assays are a fundamental departure from techniques that employ porous membranes. Chips allow true parallelism, miniaturization, multiplexing and automation, and these key features provide a set of performance specifications that cannot be achieved with the earlier technologies (see page 301, column 2)." Schena is expressly

teaching that chip assays are superior to the prior art filter based assays such as Southern blots of Orlando. Schena provides significant additional motivation to use microarrays in the place of such filter based assays noting,

"Microarray assays allow massive parallel data acquisition and analysis. Parallelism greatly increases the speed of experimental progress and allows meaningful comparisons to be made between the genes or gene products represented in the microarray. Microarray assays may eventually allow the analysis of the entire human genome in a single reaction, and recent gene-expression experiments in yeast represent an important step towards this goal. Miniaturization of conventional assays is a general trend in biomedical research. Microscale assays reduce reagent consumption, minimize reaction volumes, increase the sample concentration and accelerate the reaction kinetics. Chip-based assays allow sensitive and rapid data detection with either confocal scanners or cameras equipped with charged-coupled devices. Although current microarray assays focus on nucleic acid hybridization, future studies will undoubtedly involve the parallel analysis of proteins, lipids, carbohydrates and small molecules. Multiplexing, the process by which multiple samples are analysed in a single assay, is another enabling feature of the microarray approach. Novel labelling and detection methods, such those involving multicolour fluorescence, allow comparisons of multiple samples to be made on a single chip. Multiplexing increases the accuracy of comparative analysis by eliminating complicating factors such as chip-to-chip variation, discrepancies in reaction conditions and other shortcomings inherent in comparing separate experiments (see page 301-302)."

An ordinary practitioner, motivated by Orlando to analyze genomic nucleic acids in order to identify regions of protein binding, would have been motivated by Schena to substitute the use of a microarray for the southern blot since Schena teaches that microarrays are faster, provide more meaningful comparisons, reduce reagent consumption and accelerate reaction kinetics, as well as increasing accuracy as discussed by Schena above.

7. Claims 1-6, 8-11, 15-22, 25, 26, 28-36, 39-53, 56-59, 61-68 and 71-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mercola (U.S. Patent 6,410,233) in view of Schena (Tibtech (1998) 16:301-306).

Mercola teaches a method of claims 1, 9, 10 and 11 for identifying a region of a genome of a cell to which a protein of interest binds (see abstract) comprising the steps of:

- a) crosslinking DNA binding proteins in the cell to genomic DNA of the cell, thereby producing DNA binding protein crosslinked to genomic DNA (see figure 1),
- b) generating DNA fragments of the genomic DNA crosslinked to DNA binding protein in a), thereby producing a mixture comprising DNA fragments to which DNA binding protein is bound (see figure 1),
- c) removing a DNA fragment to which the protein of interest is bound from the mixture produced in b) (see figure 1),
- d) separating the DNA fragment identified in c) from the protein of interest (see figure 1),
- e) amplifying the DNA fragment of d) (see figure 1),
- f) combining the DNA fragment of e) with DNA comprising sequences complementary to intergenic regions of genomic DNA of the cell under conditions in which hybridization between the DNA fragments and a sequence complementary to an intergenic region of the genomic DNA occurs (see figure 1),
- g) identifying the one or more sequences complementary to the one or more intergenic regions of genomic DNA of f) to which the DNA fragment hybridizes whereby

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the region identified in g) is the region of the genome in the cell to which the protein of interest binds (see figure 1).

With regard to claims 1, 10, 11 and 71, Mercola teaches hybridization to cDNAs on a matrix (see figure 1), which is an express form of a microarray.

With regard to claims 9, 15, 16, 29-30, 46, 47, 62, 63, 77, 78, Mercola teaches the use of fluorescent labels such as Cy3 and Cy5 (see column 17, lines 60-65).

With regard to claims 2, 25, 39, 56, 72, Mercola teaches the use of cells which are eukaryotic (see column 11, line 23).

With regard to claims 3, 26, 40, Mercola teaches the use of DNA binding transcription factors (see column 11, line 6).

With regard to claims 4, 41, 57, 73, Mercola teaches crosslinking with formaldehyde (see figure 1).

With regard to claims 5, 42, 58, 74, Mercola teaches the use of antibodies to bind the protein of interest (see figure 1).

With regard to claims 6, 43, 59, 75, Mercola teaches the use of a ligation mediated PCR since the linkers must be ligated prior to PCR (see figure 1).

With regard to claims 8, 28, 45, 61, 76, Mercola teaches the use of a control (see column 19, lines 23-25).

With regard to claims 17, 31, 48, 64, 79, Mercola teaches shearing the DNA to make fragments (see figure 1).

With regard to claims 18-22, 49-53, 65-68, 80-84, Mercola teaches the analysis of the Egr-1 transcription factor control elements and genes (see example 1) where

"EGR1 belongs to a group of proteins that are involved in the progress through G1 phase of the cell cycle (see <http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=eurekah.section.11998>).

Mercola does not teach substitution of a DNA microarray with specific spots for the matrix used for detection in step (f).

Schena teaches the use of microarrays to analyze genomic information (see abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the microarrays of Schena for the blot of Mercola since Schena expressly notes "Although reminiscent of filter based assays, chip assays are a fundamental departure from techniques that employ porous membranes. Chips allow true parallelism, miniaturization, multiplexing and automation, and these key features provide a set of performance specifications that cannot be achieved with the earlier technologies (see page 301, column 2)." Schena is expressly teaching that chip assays are superior to the prior art filter based assays such as blots of Mercola. Schena provides significant additional motivation to use microarrays in the place of such filter based assays noting,

"Microarray assays allow massive parallel data acquisition and analysis. Parallelism greatly increases the speed of experimental progress and allows meaningful comparisons to be made between the genes or gene products represented in the microarray. Microarray assays may eventually allow the analysis of the entire human genome in a single reaction, and recent gene-expression experiments in yeast represent an important step towards this goal. Miniaturization of conventional assays is a general trend in biomedical research. Microscale assays reduce reagent

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consumption, minimize reaction volumes, increase the sample concentration and accelerate the reaction kinetics. Chip-based assays allow sensitive and rapid data detection with either confocal scanners or cameras equipped with charged-coupled devices. Although current microarray assays focus on nucleic acid hybridization, future studies will undoubtedly involve the parallel analysis of proteins, lipids, carbohydrates and small molecules. Multiplexing, the process by which multiple samples are analysed in a single assay, is another enabling feature of the microarray approach. Novel labelling and detection methods, such those involving multicolour fluorescence, allow comparisons of multiple samples to be made on a single chip. Multiplexing increases the accuracy of comparative analysis by eliminating complicating factors such as chip-to-chip variation, discrepancies in reaction conditions and other shortcomings inherent in comparing separate experiments (see page 301-302)."

An ordinary practitioner, motivated by Mercola to analyze genomic nucleic acids in order to identify regions of protein binding, would have been motivated by Schena to substitute the use of a microarray for the southern blot since Schena teaches that microarrays are faster, provide more meaningful comparisons, reduce reagent consumption and accelerate reaction kinetics, as well as increasing accuracy as discussed by Schena above.

8. Claims 9, 15, 16, 25, 26, 28-36, 46, 47, 62, 63, 77 and 78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Orlando et al (Methods (1997) 11:205-214) in view of Schena (Tibtech (1998) 16:301-306) and further in view of Hacia et al (Nucleic Acids Research (1998) 26(16):3865-3866).

Orlando in view of Schena teach the limitations of claims 1-6, 8, 10, 11, 17-22, 39-43, 45, 48-53, 56-59, 61, 64-68, 71-76 and 78-84 as discussed above.

While Orlando does not teach the use of fluorescent labels, Schena expressly teaches the use of multicolor fluorescence for detection (see page 302). However, neither teaches the use of Cy5.

Hacia teaches the use of a two label system where one of the labels is Cy5-phycoerythrin (see page 3865, column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the fluorescent Cy5 dye of Hacia into the detection method of Orlando in view of Schena since the use of fluorescent dyes permits replacement of the radioactive components used in Orlando and avoidance of radioactivity is desirable. Further motivation to use the Cy5 dye of Hacia is provided by Hacia, who notes "An attractive aspect of this two color system is the minimal spectral overlap between the phycoerythrin and phycoerythrin-Cy5 dyes (see page 3866, column 2)." Hacia notes that "Two color analysis allows competitive hybridization between a reference standard and an unknown sample, improving the performance of the assay (see abstract)." So an ordinary practitioner, wishing to modify Orlando in view of Schena in order to solve Orlando's concern regarding background and specificity (see page 213, column 1, where Orlando is seriously concerned with background signal in the hybridization), would have been motivated to use the two color system of Hacia since the two color system would improve signal specificity and accuracy as taught by

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Hacia (see page 3866, column 2). Further motivation to use Cy5 is that minimal spectral overlap is imposed when this dye is used in combination with phycoerythrin as discussed by Hacia.

9. Claims 23, 24, 37, 38, 54, 55, 69, 70, 85 and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Orlando et al (Methods (1997) 11:205-214) in view of Schena in view of Hacia et al (Nucleic Acids Research (1998) 26(16):3865-3866) and further in view of Hallahan et al (J. Biol. Chem. (1995) 270(51):30303-9).

Orlando in view of Schena and further in view of Hacia teach the limitations of claims 1-11, 15-22, 25-36, 39-53 and 56-68 as discussed above.

In particular, Orlando clearly teaches that the method of analysis is generic, noting "We have substantially broadened the potential of the method by adapting it to the analysis of general transcription factors (see page 205, column 2)."

Orlando in view of Schena and further in view of Hacia do not teach the species of cell cycle transcription factors.

Hallahan teach the analysis of transcription factors that are associated with cell cycle and in particular, analyzed the G1, S and G2/M transitions (see page 30304, column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to apply the method of Orlando in view of Schena and further in view of Hacia to any transcription factor, including cell cycle transcription factors such as those of Hallahan since Orlando notes "We have substantially broadened the potential of the method by adapting it to the analysis of general

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transcription factors (see page 205, column 2)." An ordinary practitioner would have been motivated to use the method of Orlando to study the transcription factors of Hallahan in order to determine where the transcription factors bind on the genomic DNA, in order to determine the higher order structure which controls gene transcription of these cell cycle factors of Hallahan.

10. Claims 23, 24, 37, 38, 54, 55, 69, 70, 85 and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mercola (U.S. Patent 6,410,233) in view of Schena and further in view of Hallahan et al (J. Biol. Chem. (1995) 270(51):30303-9).

Mercola in view of Schena teaches the limitations of claims 1-11, 15-22, 25-36, 39-53 and 56-68 as discussed above. Mercola teaches the analysis of the Egr-1 transcription factor control elements and genes (see example 1) where "EGR1 belongs to a group of proteins that are involved in the progress through G1 phase of the cell cycle (see <http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=eurekah.section.11998>).

Mercola does not teach the species of cell cycle transcription factors.

Hallahan teach the analysis of transcription factors that are associated with cell cycle and in particular, analyzed the G1, S and G2/M transitions (see page 30304, column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to apply the method of Mercola to any transcription factor, particularly cell cycle transcription factors such as those of Hallahan since an ordinary practitioner would have been motivated to use the method of Mercola to study the transcription factors of Hallahan in order to determine where the transcription factors

bind on the genomic DNA, in order to determine the higher order structure which controls gene transcription of these cell cycle factors of Hallahan.

Double Patenting

11. Claims 1-6, 8-11 and 15-26, 28-43, 45-59 and 61-86 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6,410,243 in view of Hacia and further in view of Hallahan.

Claims 1-11 of U.S. Patent No. 6,410,243 teach a method of identifying a region of a genome of a living cell to which a protein of interest binds, comprising the steps of:

a) crosslinking DNA binding protein in the living cell to genomic DNA of the living cell, thereby producing DNA binding protein crosslinked to genomic DNA;

b) generating DNA fragments of the genomic DNA crosslinked to DNA binding protein in a), thereby producing a mixture comprising DNA fragments to which DNA binding protein is bound;

c) removing a DNA fragment to which the protein of interest is bound from the mixture produced in b);

d) separating the DNA fragment identified in c) from the protein of interest;

e) amplifying the DNA fragment of d);

f) combining the DNA fragment of e) with DNA comprising a sequence complementary to genomic DNA of the cell, under conditions in which hybridization between the DNA fragment and a region of the sequence complementary to genomic DNA occurs; and

g) identifying the region of the sequence complementary to genomic DNA of f) to which the DNA fragment hybridizes,

whereby the region identified in g) is the region of the genome in the cell to which the protein of interest binds.

2. The method of claim 1 wherein the cell is a eukaryotic cell.
3. The method of claim 1 wherein the protein of interest is selected from the group consisting of: a transcription factor and an oncogene.
4. The method of claim 1 wherein the DNA binding protein of the cell is crosslinked to the genome of the cell using formaldehyde.
5. The method of claim 1 wherein the DNA fragment of c) to which is bound the protein of interest is identified using an antibody which binds to the protein of interest.
6. The method of claim 1 wherein the DNA fragment of e) is amplified using ligation-mediated polymerase chain reaction.
7. The method of claim 1 wherein the complement sequence of the genome of f) is a DNA microarray.
8. The method of claim 1 further comprising: h) comparing the region identified in g) with a control.
9. Teaches the method with the further step f) fluorescently labeling the DNA fragment of e) and i) comparing the fluorescence intensity measured in h) to the fluorescence intensity of a control, whereby fluorescence intensity in a region of the

genome which is greater than the fluorescence intensity of the control in the region indicates the region of the genome in the cell to which the protein of interest binds.

11. teaches application of the method to a transcription factor which will bind to intergenic DNA.

The claims do not teach the use of Cy5 nor do they teach the use of cell cycle transcription factors.

Hacia teaches the use of a two label system where one of the labels is Cy5-phycoerythrin (see page 3865, column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the fluorescent Cy5 dye of Hacia into the detection method of claims 1-11 of U.S. Patent No. 6,410,243 since Hacia notes "An attractive aspect of this two color system is the minimal spectral overlap between the phycoerythrin and phycoerythrin-Cy5 dyes (see page 3866, column 2)." Hacia notes that "Two color analysis allows competitive hybridization between a reference standard and an unknown sample, improving the performance of the assay (see abstract)." So an ordinary practitioner, wishing to modify claims 1-11 of U.S. Patent No. 6,410,243 would have been motivated to use the two color system of Hacia since the two color system would improve signal specificity and accuracy as taught by Hacia (see page 3866, column 2). Further motivation to use Cy5 is that minimal spectral overlap is

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imposed when this dye is used in combination with phycoerythrin as discussed by Hacia.

Hallahan teach the analysis of transcription factors that are associated with cell cycle and in particular, analyzed the G1, S and G2/M transitions (see page 30304, column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to apply the method of claims 1-11 of U.S. Patent No. 6,410,243 to any transcription factor, including cell cycle transcription factors such as those of Hallahan. An ordinary practitioner would have been motivated to use the method of claims 1-11 of U.S. Patent No. 6,410,243 to study the transcription factors of Hallahan in order to determine where the transcription factors bind on the genomic DNA, in order to determine the higher order structure which controls gene transcription of these cell cycle factors of Hallahan.

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Response to Arguments – Prior art and Double Patenting

13. Applicant's arguments filed March 9, 2006 have been fully considered but they are not persuasive.

Applicant has amended the claims to further define the microarray. In response to this amendment, a new 103 rejection is applied and most of Applicant's arguments are moot in view of the new grounds of rejection.

As noted above, Mercola remains applicable because every region is "upstream" of a transcribed region and the regions of Mercola therefore necessarily meet this requirement.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in

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the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, specific motivation is provided in the rejection, which notes "It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the fluorescent Cy5 dye of Hacia into the detection method of Orlando since the use of fluorescent dyes permits replacement of the radioactive components used in Orlando and avoidance of radioactivity is desirable. Further motivation to use the Cy5 dye of Hacia is provided by Hacia, who notes "An attractive aspect of this two color system is the minimal spectral overlap between the phycoerythrin and phycoerythrin-Cy5 dyes (see page 3866, column 2)." Hacia notes that "Two color analysis allows competitive hybridization between a reference standard and an unknown sample, improving the performance of the assay (see abstract)." So an ordinary practitioner, wishing to modify Orlando in order to solve Orlando's concern regarding background and specificity (see page 213, column 1, where Orlando is seriously concerned with background signal in the hybridization), would have been motivated to use the two color system of Hacia since the two color system would improve signal specificity and accuracy as taught by Hacia (see page 3866, column 2). Further motivation to use Cy5 is that minimal spectral overlap is imposed when this dye is used in combination with phycoerythrin as discussed by Hacia."

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Jeffrey Fredman
Primary Examiner
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